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Chronic Lymphocytic Leukemia

Epidemiological, Familial, and Genetic Aspects

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I. INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a rare neoplasm that comprises a substantial proportion of all leukemia in middle-aged persons and is the most common type among elderly persons in western populations. The major causes are not known nor is there detailed understanding about how the elusive origin(s) may relate to clinical expression, basic biological mechanisms, or pathogenesis. Nevertheless, a growing body of data exists on demographic patterns, international variation, and etiology as described in earlier reviews (1–9). Also, with the advent of rapid developments in molecular biology, information is increasing on the molecular aspects of CLL. This chapter will emphasize more recent epidemiology work, particularly for familial and genetic aspects of CLL.

Until the last 2 or 3 decades, descriptive and analytical epidemiological investigations frequently considered the leukemias as a single entity or as two major designated categories (i.e., lymphoid and myeloid) plus a heterogeneous grouping of "other and unknown." This grouping made it difficult to analyze the literature where these categories have been used. The Eighth Revision of the International Classification of Diseases (ICD) coding scheme was the first to incorporate the designations of "acute" and "chronic" for the subtypes of lymphoid and myeloid leukemia (3). In both the Eighth and Ninth (10) revisions, the three-digit ICD code 204 designates lymphoid leukemia, whereas a fourth digit is required to differentiate "chronic" (204.1) and "acute" (204.0). An extension of the ICD coding scheme for neoplasms was developed in the mid-1970s and designated as the International Classification of Diseases for Oncology (ICD-O) (11). The ICD-O included codes for morphology and anatomical site in registering incident neoplasms.

The First Edition of the International Classification of Diseases for Oncology (11) added a code for prolymphocytic leukemia (PL) to the CLL categories, whereas the second edition of ICD-O (12) added codes for adult T-cell leukemia/lymphoma and Burkitt's cell leukemia. Population-based cancer registries are increasingly reporting adult T-cell leukemia as a separate entity, but prolymphocytic leukemia is poorly ascertained and rarely reported as a separate entity by most population-based registries. Despite these advances, some recent incidence compilations and many occupational and environmental epidemiological studies do not present results using a fourth digit. Instead, these reports restrict reporting to three-digit codes (lymphocytic leukemia) or even cruder categories (such as leukemia not otherwise specified or acute versus chronic leukemia).

Recent reports show further subclassification of CLL may be appropriate (13). In 1989, the French–American–British (FAB) expert hematology group suggested guidelines for further dividing CLL into typical and atypical CLL (14). Atypical CLL includes CLL, mixed cell type, which has populations of large lymphocytes and CLL/PL, which has a mix of typical CLL cells and prolymphocytes. Molecular data now provide further support for these subcategorizations. In addition, these subtypes are characterized by clinical and prognostic differences (15). Increasingly, clinical reports categorize subtypes of CLL according to cell surface immunophenotypes and immunoglobulin expression, cytogenetic abnormalities (clonal or nonclonal aberrations, karyotype, band patterns in the major breakpoint region), molecular markers, or stage at presentation. Ideally, classifications should incorporate morphological, immunophenotypic, karyotypic, molecular, prognostic, and other features. Because standardized application of such classification approaches in all medical institutions is unlikely in the near future, it will not be possible to evaluate CLL demographic patterns to ascertain the distribution of CLL subtypes with regard to these aspects according to age, gender, racial/ethnic, or geographical differences, nor will it be possible to assess whether there is change in the distribution of CLL subtypes over time.

II. DEMOGRAPHIC PATTERNS

A. Overview

Despite availability of appropriate classification schemes to designate CLL and other subtypes according to major cell type category, newly diagnosed or incident leukemia cases reported to cancer registries and those first identified from death certificates sometimes lack complete information about subtype. For these reasons, population-based mortality data for chronic lymphocytic leukemia are generally difficult to interpret, and population-based incidence data for a given registry must be critically evaluated in light of the proportion of the total leukemia cases that are incompletely designated or unspecified according to subtype. The latter problem also complicates efforts to compare incidence rates for chronic lymphocytic leukemia among cancer registries (5–7). International data are available for various geographical regions reporting to the International Agency for Research on Cancer for the period 1988–92 (16). We selected registries to include that had larger numbers of cases, smaller proportions of unspecified or incompletely specified leukemia cases, and good-quality census data to enable accurate determination of rates. U.S. incidence patterns are summarized in the following, using data from 1973–96 from the nine population-based cancer registries (including five states and four cities comprising about

10% of the U.S. population) of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program (17).

B. International Incidence Patterns

1. Age-Adjusted Incidence Patterns

Among the four major commonly designated cell types for leukemia, variation in incidence rates was greatest for CLL (6). There was a 26-fold difference between the highest (Canada) and lowest (Japan, Osaka) age-adjusted (world standard) CLL rates for men, and a 38-fold difference between the highest (U.S., Los Angeles non-Hispanic white) and lowest (Japan, Osaka) rates for women (16). The male/female ratio ranged from 1.4 in Zurich, Switzerland, to 3.2 in Shanghai, China. High incidence rates occurred among Caucasian, non-Hispanic populations in North America (rates among men ranged from 3.35–3.69 per 100,000 per year; rates among women ranged from 1.61–1.92 per 100,000 per year), Europe (men, 2.20–3.36; women, 0.90–1.52), and Oceania (men, 2.81–2.96; women, 1.41–1.53). Low rates were seen in east, southeastern, and southern Asia among both genders (men, 0.14–0.58; women, 0.05–0.30) (Fig. 1) (16). Population-based incidence data from Asian populations, compiled in several volumes of Cancer Incidence in Five Continents by the International Agency for Research on Cancer, have demonstrated lower incidence rates for each age group than age-specific rates among other populations, but the difference between Asian and other populations is greatest at older ages. Hospital-based series from Asian populations have only infrequently been described in English-language articles, but CLL comprised only 4.6% of all leukemia among 4174 patients hospitalized at the Peking Union Medical College in Beijing, China (18). B-cell CLL incidence rates were also substantially lower among Asians than among Caucasians on the basis of reports from Japan (19). et al., 1993), China (18,20) and India (21).

C. U.S. Incidence Rates

1. Age-Adjusted Variation Among Racial/Ethnic Groups

As shown in Figure 1, highest rates within the United States in men occurred among blacks in Los Angeles, followed by whites in the SEER and Los Angeles registries, then blacks in the SEER registries, and finally Hispanics in the Los Angeles registry. For women, highest rates were among non-Hispanic whites in Los Angeles, then whites and blacks in SEER, followed by blacks in Los Angeles, and finally lowest rates in Hispanic whites in Los Angeles. Data from an earlier analysis using SEER data provide more information about other ethnic groups in that highest rates for lymphoid leukemia (not further evaluated according to acute or chronic subtypes) were seen among Caucasians, followed by African-Americans, then Hispanics and Chinese-Americans, with lowest and similar rates among Filipinos, Hawaiians, and Japanese-Americans of both sexes (data not shown) (5).

2. Age-Specific Patterns

Chronic lymphocytic leukemia is extremely rare among persons less than age 30 but increases steeply beginning in the fourth decade (Fig. 2). Rates continue to rise exponentially with increasing age and at a steeper rate of increase than other leukemia subtypes until age 70, when the rate of the increase begins to slow somewhat, particularly for black men and for women of both major racial groups. CLL is the predominant leukemia type among

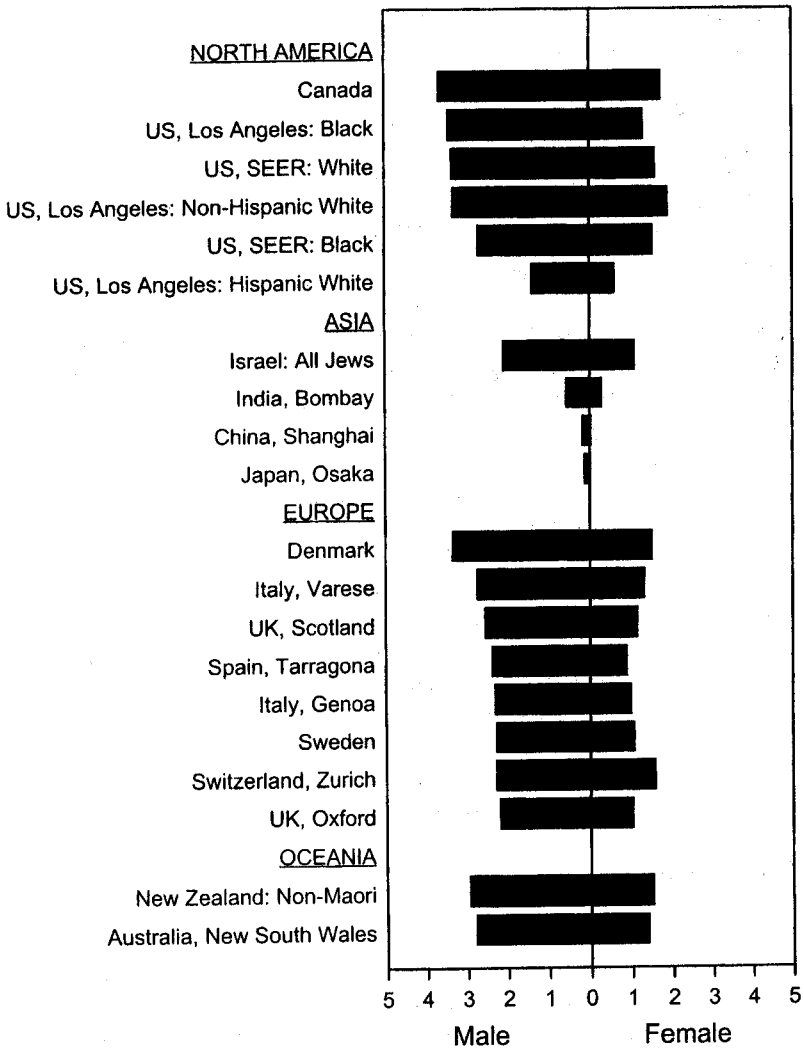

Figure 1 International incidence rates for chronic lymphocytic leukemia per 100,000 (age-adjusted, World Standard) by continent and sex, 1988–1992. (*Source*: Parkin DM, et al. Cancer Incidence in Five Continents, vol. 7. Lyon, France: IARC Scientific Publication Number 143, 1997.)

the elderly, comprising 39% of all leukemia among persons aged 65 or older (17). Incidence rates were higher among men than women at all ages (Fig. 2). For men aged 40–70, rates were similar among Caucasians and African-Americans. Among elderly men, rates were higher in Caucasians than in African-Americans. Rates for Caucasian women were slightly higher than rates for African-American women at virtually all ages. Overall, the median age at diagnosis was older for U.S. whites (66.5) than African-Americans (63.8), because of the differences in population age distribution. Age at diagnosis has risen over time in the United States with the median for all races combined rising from 65.7 years old in 1975–85 to 66.6 years old in 1986–94 (unpublished SEER Program data), largely because of the aging of the population. This pattern has also been observed

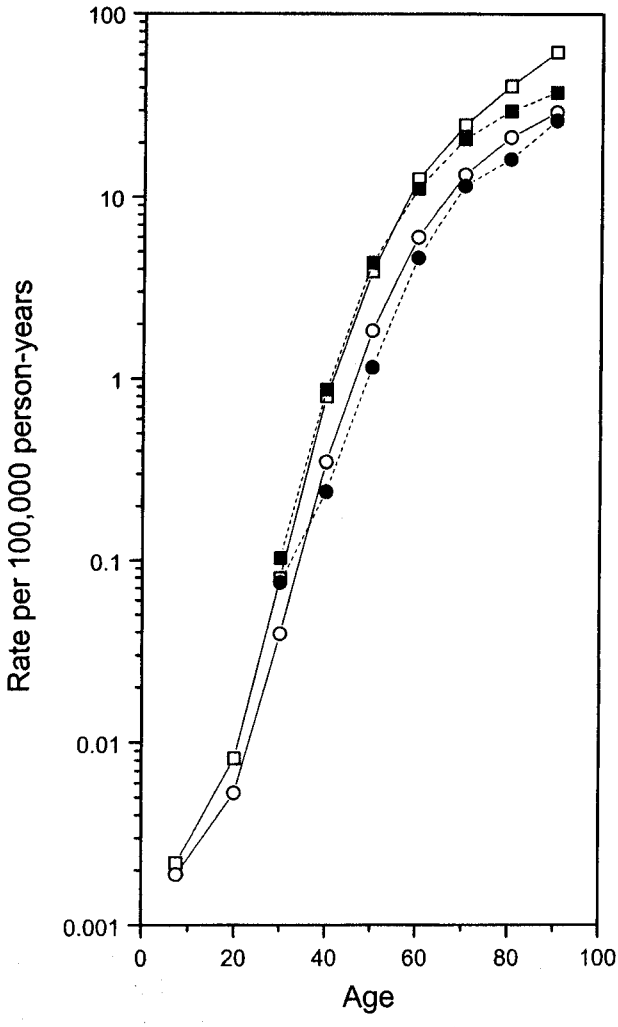

Figure 2 Age-specific incidence rates for chronic lymphocytic leukemia in the nine SEER areas by race and sex, 1973–1996. □, white male; ■, black male; ○, white female; ●, black female. (*Source*: Ries LAG, et al. SEER Cancer Statistics Review, 1973–1996. Bethesda, MD: National Cancer Institute. NIH Pub. No. 99-2789, 1999, pp 262–283.)

in other populations (22), among whom a rising proportion of patients has been diagnosed at an older age.

3. Age-Adjusted Incidence Trends

Between 1973–76 and 1993–96, age-adjusted (1970 U.S. standard) incidence rates for CLL declined somewhat in all four race-sex groups, although the trends were not linear (Fig. 3). Among Caucasian and African-American men, incidence was fairly stable between 1973–76 and 1989–92, after which incidence rates declined 20%. The decrease began earlier among females of both races. The male predominance in CLL in Western countries was more pronounced earlier in the century (reported male/female ratios ranged

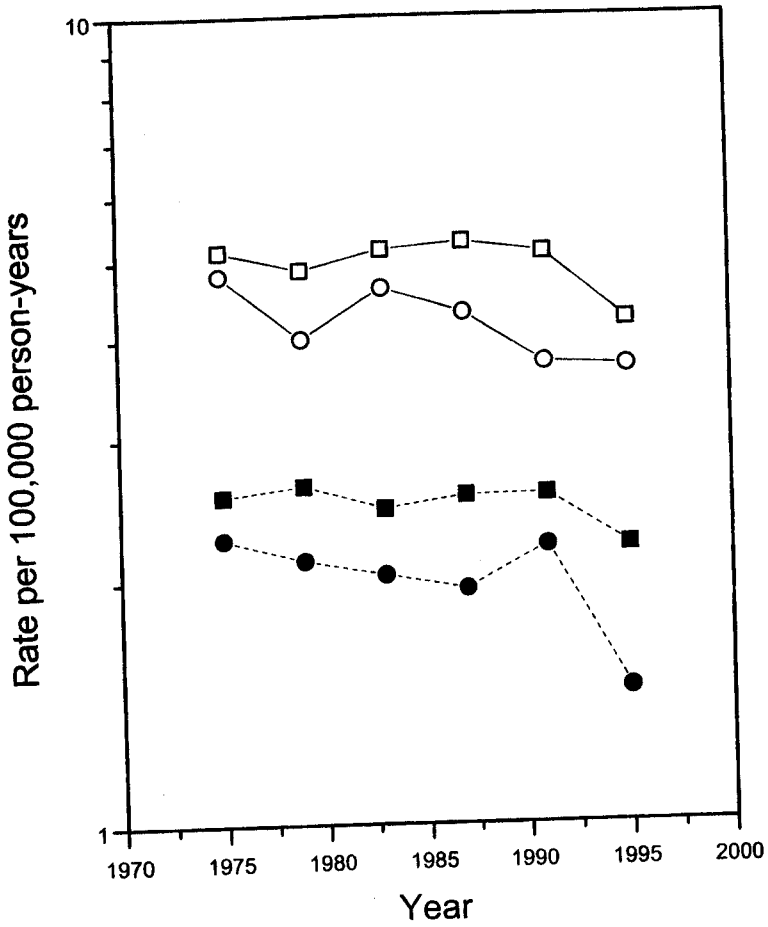

Figure 3 Age-adjusted (1970 U.S. standard) incidence trends for chronic lymphocytic leukemia in the nine SEER areas by race and sex, 1973–76 through 1993–96. □, white male; ■, black male; ○, white female; ●, black female. (*Source*: Ries LAG, et al. SEER Cancer Statistics Review, 1973–1996. Bethesda, MD: National Cancer Institute. NIH Pub. No. 99-2789, 1999, pp 262–283.)

from 2.5 to 3.0) than those reported in more recent studies (male/female ratios ranged from 1.6 to 1.9) (7).

4. U.S. Population-Based Survival Patterns

For patients with CLL in all age groups, all races, and both sexes combined, the overall 5-year relative survival increased only slightly over the 22 years monitored by the SEER Program registries, from a baseline of 68.2% in 1974–76 to 70.5 in 1989–95 (Table 1). Five-year relative survival rates were similar in Caucasian men and women but were notably lower among African-Americans, although survival was somewhat better in female than in male African-Americans. Those less than age 65 at diagnosis had a higher 5-year relative survival than persons older than age 65 at diagnosis. Interestingly, data from the population-based SEER program are somewhat more positive than data from hospital-based series. In a series of more than 105,000 patients hospitalized for leukemia in a broad spectrum of U.S. hospitals during 1985–95, patients diagnosed with CLL com-

Table 1 Five-Year Relative Survival Rates for Chronic Lymphocytic Leukemia In the U.S. SEER Program by Time Period, Race, Sex, and Age

Period	Age, race, sex	Relative survival CLL
1974–76	All ages, all races, both sexes	68.2
1989–95	All ages, all races, both sexes	70.5[a]
	Caucasian males	72.5
	Caucasian females	71.8
	African-American males	43.6
	African-American females	53.7
	Age < 65 years old	78.8
	Age 65 and older	65.9

[a] $P < 0.05$ for 1989–95 versus 1974–76.

Source: Ries LAG, Rosary CL, Hankey BF, Miller BA, Clegg LX, Edwards, BK, eds. SEER Cancer Statistics Review, 1973–1996, National Cancer Institute. NIH Pub. No. 99–2789. Bethesda, MD, 1999, pp 262–283.

prised 22.6% of the total (23). The average age of the patients in this large series was 69.6 years old at diagnosis of CLL, and overall 5-year relative survival was 48.2% and 10-year relative survival was 22.5%. Five-year relative survival progressively declined with increasing age, from 69.5% for those less than age 40 at diagnosis to 41.7% for those 80 years of age or older at diagnosis. The lower proportion that CLL comprises of total leukemia within the hospital-based (23) compared with the population-based (17) series (22.6% versus 39%, respectively) and the lower overall 5-year relative survival (48.2% during 1985–95 versus 70.5% during 1989–95, respectively), reflects the notable fraction of CLL cases that are not hospitalized for treatment because of mild or absent symptoms (24).

III. OCCUPATIONAL EXPOSURES

A. Overview

For more than 200 years, occupational exposures have been linked with an excess occurrence of cancer. Until the middle of the twentieth century, clinical observations were the primary source of information about cancers associated with occupational exposure. Historically, a specific cancer was clinically linked with a particular carcinogenic exposure when carcinogen exposure levels were high, strong statistical associations between carcinogenic exposure and cancer outcome were observed, cancer was diagnosed in workers still exposed to the putative carcinogen, and sufficient numbers of workers were affected (25).

In the second half of the twentieth century, formal epidemiological assessment was implemented using proportional mortality analysis, and then retrospective cohort studies (following up cohorts of workers retrospectively and comparing cancer risks among exposed versus unexposed groups), and case-control investigations (comparing history of occupational exposures in cancer cases versus controls). Routine surveillance to estimate the occurrence of occupationally induced cancer was initially implemented approximately 45 years ago in England and Wales. More recently, the International Agency for Research on Cancer (IARC) categorized chemical and other agents or industrial processes according to five levels. Group 1 agents were characterized by sufficient evidence of carcinogenicity

in humans. Group 2A included agents for which there was *probable* evidence of carcinogenicity in humans, and Group 2B included those with *possible* evidence of carcinogenicity in humans. Group 3 agents were those with insufficient evidence of carcinogenicity. For Group 4 agents, evidence suggested lack of carcinogenicity (26,27).

Occupational cohort studies may provide methodological advantages for evaluating potential etiological associations between CLL (or other cancers) and specific exposures. Advantages include the potential availability of long-term employment records, monitoring data for exposures and serious disease outcomes, and easier identification of potential carcinogens and processes than occurs in the residential environmental setting. Occupational exposures are often higher than those occurring in the residential setting. Nevertheless, failure to consider known nonoccupational carcinogenic exposures (such as cigarette smoking, alcohol consumption, dietary components, or infectious agents) may affect the accuracy of risk estimates for occupational exposures and associated cancers.

B. Physical Agents

1. Ionizing Radiation

Little or no evidence exists that exposure to ionizing radiation is linked with risk of CLL (28–30).

2. Nonionizing Radiation

In a comprehensive assessment of the epidemiological literature on health effects from exposure to power-line frequency electric and magnetic fields (EMF), an expert review committee concluded that there was limited evidence of a relationship between this exposure and risk of CLL. This conclusion was based on three incidence studies that incorporated measurement data (31) and 38 studies relying on job title only (32). In one of the two Swedish measurement studies, Floderus et al. (33) observed a dose-response relationship and a 3.7-fold increased risk for the 22 men whose occupational exposures to EMF were in the 90th or higher percentile of exposure among 250 male CLL cases compared with 1121 population controls. Feychting et al. (34) observed increased risks for CLL among approximately 400,000 persons residing within 300 m of a transmission line in Sweden. Risk was 1.7-fold increased among the 28 CLL cases with estimated EMF workplace exposures of 0.2 microtesla or higher and 2.1-fold increased for 2 of these 28 CLL cases with residential EMF exposures of 0.2 microtesla or greater. Theriault et al. (35) studied 223,292 Canadian and French male utility workers and found CLL risks to be nonsignificantly 1.5-fold increased among the 24 cases whose estimated occupational EMF exposures were 3.1 microtesla-years or greater and nonsignificantly 1.7-fold elevated among the six cases in the 90th exposure percentile or greater. In a meta-analysis of 38 studies of leukemia, the overall risk estimate was 1.6-fold and significantly increased for CLL (and approximately the same level of estimated risk for acute myeloid leukemia [AML]) among studies primarily relying on job title information to define exposure (32).

C. Chemical Agents and Industries with Chemical Exposures

1. Benzene

Although evidence was considered sufficient to designate benzene as a Group 1 carcinogen for acute myeloid leukemia, little evidence has implicated an association with CLL (36–38).

2. Petroleum Industry Workers

In a leukemia type-specific meta-analysis, no excess risk was found for CLL among 208,000 petroleum workers (39). A few studies have described excesses of lymphocytic leukemia or CLL (40,41) or other lymphopoietic malignancies (including non-Hodgkin's lymphoma, multiple myeloma, and possibly leukemia, cell types not specified) (40). However, Marsh et al. (42) other studies of petroleum distribution (43–46), petroleum manufacturing (47), oil and gas production (47,48) or petrochemical production (49) workers have shown no excesses.

3. Gasoline Service Station Workers

Service station workers in Nordic countries had no excess of CLL or other type of leukemia (50).

4. Rubber Workers

Benzene was used extensively in the rubber industry in earlier years, but other chemicals (some contaminated with small amounts of benzene) have been used as replacements in recent times. Excess risks of lymphocytic leukemia were observed in large cohorts of rubber manufacturing workers in the United Kingdom (51,52) and the United States (53,54). More detailed investigations linked solvent exposures of rubber industry workers with increased risk of lymphocytic leukemia (55). The specific solvents implicated included benzene, carbon disulfide, carbon tetrachloride, xylene, and others (56–58), although the notably elevated risks were based on small numbers of lymphocytic leukemia cases in the rubber manufacturing industry. More recent studies in rubber workers in the United Kingdom showed no leukemia excess (59), but a small excess was reported in a detailed review of 12 cohort studies by an IARC committee (60).

5. Styrene and Butadiene

Elevated leukemia and lymphoma risks were reported among some generally small cohorts of workers in plants producing, polymerizing, and/or processing styrene monomers and butadiene (55,61–63). Monomeric styrene and butadiene were implicated in some studies (64), whereas benzene or other solvents were more clearly linked in other investigations (65). No leukemia excesses were observed in large cohorts of workers employed in styrene-butadiene polymer manufacturing and reinforced plastics and composites (styrene-exposed) manufacturing plants (66–68). A notable excess of leukemia among workers exposed to butadiene, but not styrene, in a nested case-control study may indicate a causal association, or possibly a chance of confounding (69). In a retrospective cohort study of 40,683 workers in the reinforced plastics industry from Denmark, Finland, Italy, Norway, Sweden, and the United Kingdom, information on exposure to styrene was reconstructed through job histories, environmental and biological monitoring data, and production records of the plants. There were no excesses of all cancers or of neoplasms of the lymphatic and hematopoietic tissues overall, nor did risk increase with increasing length of exposure. However, mortality from leukemia and lymphoma rose with time since first exposure to a twofold excess 20 years after first exposure (70). Small excess risks of lymphohematopoietic cancers were found in some studies of 1,3-butadiene production facilities (71) particularly among long-time workers. Workers employed in the 1960's in companies producing reinforced plastics in Denmark had elevated risks (72).

6. Ethylene Oxide and Related Chemicals

Ethylene oxide was designated as a probable human carcinogen on the basis of elevated risks for lymphatic leukemia and lymphoma observed in three small Swedish cohorts (73–76) and animal carcinogenicity data (77). Subsequently, excesses of lymphoid leukemia and lymphoma and a significant dose-response effect for these neoplasms were observed among U.S. workers in this industry (78). Non-Hodgkin's lymphoma (but not leukemia) was significantly elevated among U.S. workers from 14 plants producing sterilized medical supplies (79), and elevated leukemia risks were linked with production of ethylene or propylene chlorhydrin, rather than ethylene oxide, at two U.S. facilities (80,81). No excesses were seen in German (82), British (83), or other U.S. plants (84,85), however, leading to an assessment that available data do not provide convincing or consistent evidence of leukemogenicity (86). It is possible that CLL may be linked with ethylene oxide exposure in view of the excess risks seen for non-Hodgkin's lymphoma (NHL) and lymphoid leukemias in those studies evaluating these endpoints. However, investigations focusing on total leukemia mortality could fail to identify excess risks of CLL even if the increases are real because death certificates are often lacking specification of cell type of leukemia.

7. Chemists and Workers in Medical Research

Small excesses of lymphopoietic malignancies (often including a combination of CLL, NHL, and sometimes other neoplasms such as Hodgkin disease or multiple myeloma) have been reported among chemists (87) and workers in biomedical research (88), science technicians (89), clinical laboratory technicians (working in analytical chemistry, pathology, cytology, genetics, and other laboratories) (90), and workers in other types of laboratories (91), but specific chemicals or infectious agents that might be responsible have not been identified. Although excess risks of lymphopoietic tumors have been linked with a high probability of exposure to chemicals, other possibilities could not be ruled out. In most of these studies, risks for CLL have not been separately evaluated from risks for total leukemia.

D. Farmers and Other Agricultural Workers

Many, but not all, studies have shown associations between all types of leukemia and farming (7,92,93). A substantial proportion of the studies have evaluated mortality for all leukemia types combined, although investigations examining risks according to leukemia cell type have implicated farming or farm-related exposures in risk of CLL (94–96). Specific agricultural exposures linked with elevated risk of CLL include DDT (97), animal breeding (98), and working in flour mills (99). Blair and Zahm (93) have postulated that agricultural exposures might affect the immune system. Other agricultural exposures that may be leukemogenic include various agrochemicals (including crop and animal insecticides, herbicides, and fertilizers), infectious agents, or other exposures associated with various forms of livestock, fertilizers, and certain crops. Forage growing and organophosphate insecticides have been associated with elevated risk of hairy cell leukemia (100).

E. Other Occupational Exposures

In a few studies, CLL has also been linked with working in underground coal mining (101), carpet manufacturing (102,103), sawmills or industries using lumber products (27,104), and employment as a barber or hairdresser (105,106) or as a vehicle mechanic (107). Limited data also support associations between CLL and exposure to asbestos (108,109), brick mortar (110), and wood products (97,111).

IV. ENVIRONMENTAL AND LIFESTYLE EXPOSURES

A. Environmental Exposures

There are few studies assessing risks of environmental exposures. Comprehensive assessments have concluded that nonoccupational, environmental exposures to ionizing radiation and nonionizing radiation are not associated with increased risk of CLL (28–31). Although CLL was modestly increased in some studies of farmers and agricultural workers, there is no consistent evidence linking residential pesticide exposures to increased risk of CLL.

1. Cigarette Smoking

Although cigarette smoking has been established as an important risk factor for lung cancer for several decades, it was not until 1986 that smoking was initially linked with increased risk of leukemia (112). An increasing number of cohort and case-control studies reveal increased risks of AML associated with cigarette smoking (7), whereas only three cohort investigations demonstrated elevated risks of lymphocytic leukemia (113–115). One case-control study also demonstrated an increased risk of CLL (116) associated with cigarette smoking. Recent large cohort studies have demonstrated no evidence of an association between cigarette smoking and CLL (117,118).

B. Lifestyle Factors

1. Hair Dyes

CLL, AML, total leukemia, and myelodysplastic syndrome (MDS) have been linked with employment in cosmetology in some investigations (7,119). Risk of CLL was not elevated among men or women using hair dyes in a population-based case-control study in Nebraska (120), nor in large cohorts of women (121) or men and women (56,57,122,123).

2. Diet and Other Lifestyle Factors

There has been little effort to evaluate other potential risk factors for CLL, such as diet or physical activity. In the absence of compelling clinical reports or other evidence linking such factors with CLL, it is unlikely that hypothesis-testing studies will evaluate these factors in the near future.

V. PRIOR MEDICAL HISTORY

The role of prior medical illnesses in the subsequent development of CLL has been investigated in epidemiological studies. Biological hypotheses suggest that infections, allergies, and autoimmune disorders may be associated with long-lasting effects on the immune system, particularly on the B-cell lymphocytes. Autoimmune diseases (lupus erythematosus, multiple sclerosis) may also predispose to CLL given that there is chronic immune dysregulation either arising from or leading to perturbations of lymphocytes.

In a large U.S. case-control study, no association was found between vaccinations or allergy desensitization shots and CLL (124). A small risk of CLL was linked with a history of three infections: syphilis, tuberculosis, and urinary tract infections. The investigators suggested that the association with syphilis might be due to the former use of arsenic in treatment regimens. They also found a small increased risk of CLL associated with history of appendectomy or tonsillectomy. A case-control study of leukemia in Shanghai, China (125) also showed an association with appendectomy; however, because CLL is rare in Asia, the case number was very small. This study also reported associations of

CLL with rheumatoid arthritis, hyperthyroidism, asthma, eczema, chronic infections other than tuberculosis, and use of salicylates. A positive association with prior use of diagnostic x-rays was also reported. In contrast, a case-control study in Yorkshire, England (126), found no association with appendectomy but did find an increased risk of CLL linked with history of migraine, scarlet fever, chronic ear infection, bronchitis, hypertension, and myocardial infarction and a recent history of herpes zoster and a history of malignancy. A large case-control study (127) found no association between various infections and autoimmune disorders and subsequent risk of CLL. However, the investigators reported a small protective effect for allergy-related disorders and surgical ablation of lymphoid tissue. Another case-control study on individuals from California found a decreased risk for CLL in patients with a history of rheumatoid arthritis (RR = 0.3) (128). The investigators also looked at risk of CLL and previous history of tuberculosis, bronchitis, hay fever, eczema, rheumatic fever, and musculoskeletal disease and found no associations.

Overall, results from studies assessing prior medical conditions or treatments and risk of CLL have shown no clear, consistent relationships. In the absence of consistent findings or intriguing clues, it is unclear that this approach is likely to be productive.

VI. FAMILIAL CLL

A family history of CLL or other lymphoproliferative disorders is one of the strongest risk factors for development of CLL. For more than 40 years, familial clustering of CLL, whether with other cases of CLL or other lymphoproliferative disorders, has been reported. In 1947, Videbaek published his seminal work on familial leukemia (129). Videbaek observed that the percentage of lymphoid leukemia was almost double that of myelogenous leukemia in the familial cases. Nearly 30 years later, Gunz published his study of more than 900 individuals in Australia with leukemia (130) and reported findings consistent with Videbaek in that first-degree relatives with leukemia were more frequent in families of cases with CLL than in those with CML. There have subsequently been numerous reports of familial aggregations of CLL (131–137).

Case-control studies show increased risks of leukemia and lymphoproliferative disorders among relatives of cases with CLL (138–140). The etiological factors responsible for these aggregations, whether genetic, shared environmental factors or a combination of both, remain to be explained. Data on possible candidate genes for CLL is reviewed in the following section. One interesting phenomenon observed in CLL is anticipation. Anticipation refers to the worsening severity or earlier age of onset in successive generations (141). Three separate groups of investigators have now reported observing anticipation in familial CLL. Horwitz et al. (141) first described this finding in CLL and AML families, showing a significant difference between the mean age at onset of leukemia in the parental generation and mean age at onset in affected individuals in the offspring generation (66 years versus 51 years). Yuille and colleagues confirmed this finding in 1998 (142), reporting a mean difference in average age of onset between generations of 22.1 years. Goldin et al. (143) observed a similar decrease in average age of onset of CLL between generations (66.7 years versus 50.7). To rule out a bias from changes in clinical screening practices, conservative assumptions about age of onset and information on extrapolated stage at diagnosis were included in the analyses. With this approach, the investigators did not find evidence for temporal changes in clinical screening practices as an explanation for anticipation. Although changes in clinical screening patterns may affect

age at diagnosis, this does not appear to be the sole explanation for the observation of anticipation.

Anticipation has been reported in familial occurrence of numerous serious chronic diseases (144). One of the more quoted examples is Huntington disease, in which expansion of trinucleotide repeats (sequences of repeated amino acids) is shown to occur in younger and younger persons in subsequent generations (145). Whether similar genetic alterations may play a role in the anticipation in CLL remains to be determined.

VII. GENETICS OF CLL

Family studies are often the method whereby candidate disease genes are identified. A rapidly expanding body of literature documents genetic changes found in CLL. To date, no specific "CLL gene" has been identified, and the molecular pathogenesis of this disease remains largely unknown. Numerous reports on molecular abnormalities in CLL are helping to better delineate prognosis, including survival and response to treatment. This information may aid in therapeutic decision making. In addition to the relationship of specific genetic abnormalities to prognosis, it is also possible that an unknown fraction of genetic abnormalities associated with CLL may also be of etiological importance. This section will review the existing literature on genetic abnormalities associated with CLL from the epidemiological perspective. This information is summarized in Table 2. The reader is also referred to Chapters 2 and 16, which address molecular biology and chromosomal abnormalities of CLL.

A. Chromosome 6

Philip and colleagues evaluated chromosome 6 abnormalities in newly diagnosed cases of CLL using banding techniques (146). The investigators demonstrated alterations in 6% (11 of 193) cases: five cases showed 6p rearrangements, and six cases showed 6q rearrangements. This study also reported that cases with 6q aberrations were diagnosed at a significantly later stage at diagnosis compared with cases without 6q aberrations but this did not translate into a difference in survival. More recent studies point to three areas on the long arm of chromosome 6 that may be the regions of interest in CLL: 6q11-21, 6q21-23, and 6q25-27. Among 285 B-CLL cases evaluated using interphase fluorescent in situ hybridization (FISH), 7% (21 of 285) had 6q21 deletions and 3% (6 of 205) had 6q27 deletions (147). The six cases with 6q27 deletions also had 6q21 deletions. Clinical evaluation showed that patients with 6q deletions had higher white blood cell counts and greater lymphadenopathy compared with patients without 6q deletions, although overall survival did not differ. In a small study from Israel, Amiel et al. (148) found 6q27 deletions in 3 of 14 CLL patients. It is unclear what candidate gene exists at locus 6q21, although recently the TLX gene (a member of the steroid nuclear receptor family and potential tumor suppressor gene) was localized to this region (149).

B. Chromosome 11

Several gene regions on chromosome 11 are of interest as susceptibility loci for CLL. The *ATM* (mutated in ataxia-telangiectasia) gene located at region 11q22-q23 has been investigated as a putative CLL gene. Ataxia-telangiectasia is a rare, autosomal recessive disease characterized by phenotypic pleiotropy, which includes cerebellar degeneration

Table 2 Summary of Genetic Studies of CLL

Authors/year	Study population	Chromosomal abnormality	Method	Cases evaluated	Positive cases *n* (%)
(Philip et al., 1991)	Denmark	Chromosome 6	G-banding	193	11 (6)
(Gaidano et al., 1994)	Italy	6q27	Southern blot	100	4 (4)
(Amiel et al., 1999)	Israel	6q27 (deletion)	FISH	14	3 (21)
(Stilgenbauer et al., 1996)	Germany	6q21	FISH	285	21 (7)
		6q27		208	6 (3)
(Sola et al., 1999)	France	11q13 [t(11;14)] (Bcl 1/PRAD1 gene)	Rt-PCR and Western blot	111	4 (3)
(Gaidano et al., 1994)	Italy	11q13 [t(11;14)]	Southern blot	100	0
(Cuneo et al., 1997)	Italy	11q13 [t(11;14)]	G-banding and FISH	57	14 (25)
(Stankovic et al., 1999)	United Kingdom	11q22-23 (ATM)	Rt-PCR and Western blot	32	6 (18) (8/20 cases had decreased ATM protein)
(Dohner et al., 1997)	Germany	11q22-23	FISH	214	43 (20)
(Dohner et al., 1993)	Germany	12 (trisomy)	FISH	42	6 (14)
(Que et al., 1993)	United Kingdom	12 (trisomy)	FISH	183	21 (11)
(Cuneo et al., 1994)	Italy	12 (trisomy)	FISH	42	6 (14)
(Criel et al., 1994)	Belgium	12 (trisomy)	G-banding and FISH	111	16 (14)

(Avet-Loiseau et al., 1996)	France	12 (trisomy)	FISH	100	16 (16)
(Woessner et al., 1996)	Spain	12 (trisomy)	FISH and G-banding	61	7 (12)
(Gahn et al., 1997)	Germany	12 (trisomy)	FISH	75	15 (20)
(Criel et al., 1997)	Belgium	12 (trisomy)	G-banding	296	32 (11)
(Geisler et al., 1997)	Denmark	12 (trisomy)	G-banding	480	40 (8)
(Acar and Connor, 1998)	Turkey	12 (trisomy)	FISH	26	4 (15)
(Nair et al., 1998)	India	12 (trisomy)	FISH	60	37 (62)
(Liso et al., 1999)	Italy	12 (trisomy)	FISH	23	6 (26)
(Garcia-Marco, 1996)	United Kingdom	13q12	FISH and G-banding	35	28 (80)
(Liu et al., 1992)	Sweden	13q14 (RB1 gene)	Q-banding and Southern blot	27	3 (11)
(Kroft et al., 1997)	United States	13q14	FISH and G-banding	78	23 (30)
(Gahn et al., 1997)	Germany	13q14 (RB1 gene)	FISH	30	6 (20)
(Stilgenbauer et al., 1998)	Germany	13q14	FISH	322	75 (23) RB1 121 (38) D13S25
(Hogan et al., 1999)	United States	13q14	FISH	54	26 (48)
(Avet-Loiseau et al., 1996)	France	13q14	FISH	100	31 (31)
(Geisler et al., 1997)	Denmark	Chromosome 17 (17p and 17q	G-banding	480	8 (2)
(Dohner et al., 1997)	Germany	17p53	FISH	214	21 (10)
(Gaidano et al., 1994)	Italy	17q13 (p53 gene)	SSCP and direct sequencing	100	10 (10)

with progressive ataxia, oculocutaneous telangiectasias, immunodeficiency, sensitivity to ionizing radiation, and a notable predisposition to malignancy (150–152). There is 100-fold increased risk of cancer in patients with AT, and approximately 10% to 15% of patients who are ATM homozygotes develop a lymphoproliferative malignancy (153). Dohner demonstrated 11q22–23 deletions in 20% of cases with CLL (154).

Estimates of 11q deletions in sporadic B-CLL range from 20% to 32% (154,207). Studies of loss of heterozygosity (LOH) in ATM loci have shown 14% to be affected at various markers (155). LOH studies have shown that CLL cases with ATM mutations appear to have more aggressive disease and poorer survival (154). ATM protein expression appears to be markedly decreased in individuals with ATM deletions, and these individuals have shorter survival times than patients with normal ATM protein levels (155). This study showed that survival was significantly shorter in patients less than 55 years of age who also had decreased levels of ATM protein expression. A linkage study of ATM in 24 CLL families did not find evidence for an association (156).

Another site of interest on chromosome 11 is 11q13, the site of the PRAD/cyclin D1. The translocation t(11;14) (also known as BCL1 translocation), which brings the cyclin D1 gene under the control of the IgH gene located at 14q32, is now recognized as a hallmark molecular change in mantle cell lymphoma (157). A few studies have demonstrated this translocation in CLL cases (158,159) and it may be associated with atypical CLL (158) or with cases of poorly characterized B-cell chronic lymphoproliferative disorders (157).

C. Chromosome 12

Trisomy 12 is the most common chromosomal aberration seen in B-CLL with various reports citing 8% to 62% of cases affected (160–166, 208–210). FISH appears to be a more sensitive method for detecting chromosome 12 abnormalities compared with traditional banding techniques (161,162). Trisomy 12 has been associated with poorer survival (160) and with atypical lymphocyte morphology (167–170). It is not yet clear what region of chromosome 12 may be linked with B-CLL, but reports implicate band 12q13 as the site of the potential gene(s) (171,172). Although CLL is thought to be an abnormality of mature B-cells, one study has shown trisomy 12 detectable in CD34+/CD38+ hematological progenitor cells in a subset of CLL patients (165).

D. Chromosome 13

Abnormalities in chromosome 13 are the second most common abnormalities occurring in CLL, occurring in 11% to 48% of cases studied (see Table 2). Initial studies of chromosome 13 abnormalities in CLL seemed to point to the retinoblastoma gene (RBI)—a tumor suppressor gene located at 13q14 (163,173). However, further investigations suggest that alternate loci in the 13q14 regions including D13S25 (174–177), a region in close proximity to the RB1 gene, may in fact be the site of a novel tumor suppressor gene(s) involved in CLL. Another locus, D13S272 in the region of 13q14 and located very close to the *Leu* 1 and *Leu* 2 (leukemia-associated gene 1 and 2), has also been suggested as the site of tumor suppressor gene(s) involved in CLL (178,179); however, another investigation was not able to confirm this finding (180). Although most studies of chromosomal abnormalities in CLL examine peripheral blood lymphocytes and bone marrow lymphocytes, Gahn et al. studied 13q14 deletions in CD34+ selected progenitor cells (165). His group

found that 20% of cases carry a 13q14 deletion in these stem cells, suggesting that pluripotent stem cells may undergo clonal transformation in CLL.

Some studies have shown 13q14 abnormalities to be associated with typical lymphocyte morphology in CLL (181), whereas others have not shown any clinical correlation with 13q14 changes (163). Starostik et al. found no difference in survival between patients with and without LOH at 13q14 (182). However, in patients with low β_2-microglobulin levels, individuals with LOH at 13q14 had significantly shorter survival than individuals without LOH, but these results were based on small numbers. When analyzed by stage, early-stage patients (Rai 0-II) with 13q14 LOH had a significantly shorter survival. Hogan showed that individuals with monosomy in the 13q14 region (RB1, D13S319, or D13S25 loci) had a longer treatment-free survival than individuals with diploidy at these loci, although the difference was not statistically significant (183). The other region of interest on chromosome 13 is the BRCA1 gene, encompassing 13q12; however, data on the role of this region have been mixed (184,185).

E. Chromosome 17

The p53 tumor suppressor gene, located at 17p13.1 is the most common genetic abnormality in cancer, and mutations of p53 have been associated with the Li-Fraumeni syndrome (186). However, p53 abnormalities appear to be infrequent findings in sporadic CLL (187). Approximately 10% of CLL cases are reported to have p53 abnormalities (154,188), and Gaidano et al. showed that these were due to mutations in the p53 gene rather than inactivation of p53 by amplification of the MDM2 gene. Mutations in p53 may be a more frequent finding in atypical subtypes of CLL such as CLL-PL (CLL-prolymphocytic subtype) (189), and it is possible that p53 plays a role in transformation of CLL to intermediate or high-grade non-Hodgkins lymphoma (190).

F. Immunoglobulin Gene Rearrangements and CLL

Until recently, B-CLL was thought to arise from naïve B-lymphocytes as demonstrated by germline configurations of V_H immunoglobulin gene sequences. New observations show that V_H genes may be either mutated or unmutated and that this finding may represent a novel prognostic indicator. Hamlin (191) evaluated 84 patients with CLL and found that 45% of cases had unmutated V_H genes and 55% had mutated V_H genes. Clinical correlation showed a significant correlation with mutation status: among stage A patients, individuals with mutated V_H genes had a median survival of 293 months compared with individuals with unmutated V_H genes who had a median survival of 95 months. Two groups have looked at V_H gene use in familial CLL. One group evaluated 12 families (Italian and French) and found that gene use was nonrandom and differed from frequencies reported among nonrelated patients (192). In contrast, another group evaluated 11 families (United States) and found a pattern of V_H gene use similar to sporadic CLL cases (193). These findings suggest that B-CLL is indeed a heterogeneous disease, not only at the clinical level but at the molecular level as well, and that CLL may arise from either memory B-cells or naïve B-cells.

G. Telomeres, Telomerase, and CLL

Telomeres are present on the end of eukaryotic chromosomes and function to prevent chromosome instability and DNA degradation. Telomeres are repeated amino acid se-

quences that are synthesized by the enzyme telomerase. Shortened telomeres and increased telomerase activity may play a role in human tumors. Several studies have looked at the relationship of telomere length and telomerase activity in CLL. Bechter et al. (194) showed that shorter telomere length was associated with a significantly shorter survival, and higher telomerase activity was observed in patients with more advanced disease. Trentin et al. (195) found higher telomerase activity in CLL versus normal lymphocytes, and higher activity was more often found in individuals with progressive rather than stable disease.

Although no single gene has been identified as a susceptibility gene for CLL, it is clear from mounting data that several chromosomal regions repeatedly show abnormalities. It is possible that one of the genes described earlier is in fact the "CLL gene," whereas the others play a role in the carcinogenesis pathway for CLL development. Another possibility is that CLL may be more heterogeneous than previously recognized and that multiple genetic paths can lead to the same phenotypic outcome—the development of CLL. Therefore, it is important in future genetic studies to continue to make clinicopathological correlations in an effort to better understand the genetic events that lead to CLL. In addition, because epidemiological studies of CLL seek to identify exposures that are etiologically associated with CLL, it will undoubtedly be useful to evaluate whether specific exposures are etiologically linked with distinct genetic abnormalities that characterize CLL, particularly those that are found to play an important role in the pathogenesis of this malignancy.

VIII. SECOND MALIGNANCIES SUBSEQUENT TO CLL

Because CLL is a cancer of the immune system, and immune dysfunction has been posited to play a role in carcinogenesis, second cancers may play an important role in the natural history of CLL. Second cancers may be particularly important in those patients with indolent CLL or early-stage disease, whose survival might otherwise be similar to those without CLL. Also of interest is whether therapy for CLL may play a role in development of second cancers.

Numerous case reports of second malignancies after CLL and more than 15 studies of populations of CLL patients with second malignancies have been published in the literature. Seven studies will be the focus of review here (Table 3). In addition, several studies have evaluated either specific types of cancer after CLL (e.g., lung, renal) or second malignancies after a specified treatment (fludarabine). These studies will also be mentioned in the text portion only of this section. Studies of second malignancies after CLL vary in numbers of primary CLL patients and method. Some authors chose to exclude cases that were diagnosed simultaneously with CLL and another malignancy or within 3 to 6 months of the diagnosis of CLL. Even if CLL is diagnosed simultaneously or shortly before a second malignancy, CLL could have existed for several years before diagnosis. Although the origins of CLL and a second malignancy may differ, a common etiological agent could contribute to both. Several studies had treatment data available and analyzed the contribution of this factor to development of second tumors.

Of the seven studies listed in Table 3, three are population based and four are hospital based. The studies are based on populations from Canada (196,197), the United States (198–200), and Europe (201,202). Numbers of CLL cases varied from 102 to 9456, and the range of second cancers diagnosed in each study was 13 to 840. The rates for second cancers ranged from 6.2% to 15.7%. In addition, in studies with small numbers of second tumors, the cancer subtype analyses may be based on a few cases only. The person-year

Table 3 Summary of Studies of Second Malignancies in CLL

Authors/year	Number of cases of CLL/study population	Type of registry	Total number of second malignancies	Relative risk (RR) of second malignancy (observed-expected ratio)
(Stavraky et al., 1970)	n = 258 (825 person-years)/Canada	Hospital	13	1.29 (for all sites) 1.89 (skin only)[a]
(Manusow and Weinerman, 1975)	n = 102 (395 person-years)/Canada	Hospital	16	3.18 (all sites) 8.14 (skin only)[a]
(Greene et al., 1978)	n = 4869 (16,584 person years)/United States	Population	234	1.1 (all sites) 6.7 (melanoma) 5.3 (connective tissue) 1.5 (lung)
(Davis et al., 1987)	n = 419 (1399 person years)/United States	Population	57	2.3 (non-lymphoid) 22.5 (soft tissue)[b] 4.2 (lung) 3.3 (colon) 2.7 (other sites) 5.6 (lymphoid)
(Travis et al., 1992)	n = 9456 (39,943 person-years)/United States	Population	840	1.28 (all sites, excluding NHL) 7.69 (Hodgkins disease) 3.97 (eye) 2.79 (melanoma) 1.98 (brain and central nervous system) 1.90 (lung) 1.20 (prostate) 1.51 (other ill-defined or unknown sites)
(Bertoldero et al., 1994)	n = 212/Italy	Hospital	19	1.4 (all sites) 16.7 (tongue)[c] 10 (thyroid)[c] 10 (gallbladder)[c] 3.5 (lung)
(Lauvin et al., 1996)	n = 248/France	Hospital	22 (non-lymphoma)	Risks not calculated (see text)

[a] Subtypes of skin cancer not given.
[b] Based on 2 cases.
[c] Based on 1 case.

follow-up ranged from 395 person-years to 39,943 person-years and was not given in two studies. With regard to gender, most of the studies showed risk of a second cancer not to be significantly different for men and women. Six of the seven studies calculated risk ratios on the basis of observed versus expected number of cancer cases. The two earliest studies give risks for skin cancer only, but the subtypes of skin cancer are not given, so comparison to later studies that tend to separate melanoma from nonmelanoma skin cancer is difficult. Most studies included second hematopoietic malignancies in the analyses; however, because cases of non-Hodgkins lymphoma and possibly other B-cell neoplasms may represent a clonal evolution of the underlying B-CLL, it may be more appropriate to exclude these types of cancers. Recent evidence shows that Hodkgin's disease (HD) arises from the B-cell lymphocyte (203). It is possible that HD after CLL represents a disease transformation or clonal selection similar to Richter syndrome.

All of the studies in Table 3 showed consistent increases in second malignancies of all sites, with risks ranging from 1.1 to 3.18. Davis et al analyzed lymphoid malignancies separately from nonlymphoid malignancies and found an increased risk of 5.6 for NHL, HD, and multiple myeloma (199). Travis et al. also found an increased risk for HD of 7.69 based on 13 cases (200). The risk of lung cancer as a second primary tumor was elevated in four of the studies, with risks ranging from 1.5 to 4.2 (198–201). Soft tissue sarcomas and connective tissue tumors were noted to be elevated in two studies with risk of 5.3 (198) and 22.5 (199); however, the second study is based on only two observed cases. Two studies showed elevated risks for skin cancer of 1.89 and 8.14; however, subtypes (basal cell, squamous cell, melanoma) were not given (196,197). Two studies showed elevated risks of 2.79 and 6.7 for melanoma (198,200), and Travis et al. also found an elevated risk of 3.97 for ocular melanoma (based on four cases) (200). Chemotherapy and radiation may have contributed to the increased risk of melanoma, lung cancer, and HD (198,200).

In a cohort of young ($\leq$ 55 years old) CLL patients in Italy observed over a 10-year period, Mauro and colleagues found a second cancer rate of 4% compared with 14% among an older ($>$ 55 years old) CLL cohort (204). The investigators also noted a similar rate of second malignancies between both treated (9.5%) and untreated (11%), although a higher rate of Richter's transformation (5.9% versus 1.2%) was seen among younger cases. Nucleoside analogues, primarily fludarabine, are now an important part of CLL treatment. Two large studies have reported follow-up of patients who have received either fludarabine or other nucleoside analogues for CLL. Among 174 patients treated with fludarabine as initial therapy between 1986 and 1993, six individuals (3%) died of second malignancies: liver cancer (n = 1), lung cancer (n = 2), ovarian cancer (n = 1), colon cancer (n = 1), and head and neck cancer (n = 1) (205). In the same study, one patient had HD develop, and nine patients had a Richter's transformation develop. In another study, Cheson et al. reviewed data on 724 patients who had received fludarabine for relapsed and refractory CLL (206). Among the 595 individuals for whom information on second malignancies was available, 83 (14%) second malignancies were reported. However, when NHL (18 cases), nonmelanotic skin cancer (3 cases), cancers diagnosed before or within 2 months of starting fludarabine (36 cases), or with a missing diagnosis date (3 cases) were excluded, this number fell to 23. With these exclusions, an excess risk of second cancers (1.65) was still seen. Of these 23 second cancers, the highest number of second tumors included lung (n = 6), gastrointestinal (n = 5), and bladder (n = 2). No cases of melanoma were reported, and 1 case each of sarcoma and CNS cancer was observed.

The risk of second malignancies appears consistently increased among individuals with CLL. There may be a higher rate of melanoma, sarcoma and other connective tissue

cancers, lung, and colon cancer, although these increases have not been as consistently observed, and small numbers of cases make risk ratios somewhat unstable. Although treatment may play a role in this increased risk, it does not solely explain the rate of second malignancies, which are also seen among untreated patients. In addition, fludarabine does not appear to pose any greater risk than older treatments such as chlorambucil. It is likely that a combination of immune dysregulation, which is intrinsically part of CLL, underlying genetic alterations, and environmental and lifestyle exposures (such as benzene and cigarette smoking), may contribute to the development of second cancers.

IX. SUMMARY

In summary, research has led to an improved understanding of the natural history and biology of CLL. Within the past 20 years, the heterogeneity of the disease has become clear based on clinical observation. Advances in molecular biology are leading to insights into the genetic changes that accompany CLL. Despite all the progress, much remains to be understood about this disease. Although there are certain suspect etiological exposures such as certain prior medical conditions, the associated risks have not been overwhelmingly large or consistent. New techniques to evaluate small and complex chromosomal changes seem to pinpoint several possible candidate gene regions for CLL. In the coming years, future research should focus on better understanding the clinical heterogeneity of CLL and attempting to explain the specific molecular markers that may be important in defining etiologically distinct subtypes of the disease. Rather than there being a single pathway to the development of CLL, it is more likely that there are multiple potential leukemogenic pathways with various environmental and genetic factors interacting. Future epidemiological studies of environmental and other risk factors should attempt to include biospecimen collection as part of the study in an effort to identify "at-risk" phenotypes—that is, certain individuals who may be more susceptible to carcinogenic effects of certain agents.

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